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Originally published at:
Regoli, F; Denegri, A; Moccetti, T (2014). The peri-procedural management of new oral anti-coagulants (NOACs) in interventional electrophysiology. Experimental and Clinical Cardiology, 20(10):6088-6108.

EXPERIMENTAL & CLINICAL
Cardiology

EXPERIMENTAL & CLINICAL CARDIOLOGY

Volume 20, Issue 10, 2014

Title: "The peri-procedural management of new oral anti-coagulants (NOACs) in interventional electrophysiology"

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How to reference: The peri-procedural management of new oral anti-coagulants (NOACs) in interventional electrophysiology/Francois Regoli, Andrea Denegri and Tiziano Moccetti/Exp Clin Cardiol Vol 20 Issue10 pages 6088-6108 / 2014

Experimental & Clinical Cardiology

The peri-procedural management of new oral anti-coagulants (NOACs) in interventional electrophysiology

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Abstract

Because of their rapid onset of action and short therapeutic half-life, new oral anticoagulants (NOACs) may significantly simplify peri-procedural oral anti-coagulation management during cardiac implantable electronic device implant and trancatheter ablation procedures. The pharmacological properties of NOACs are reviewed to better comprehend how these drugs may best be managed in the setting of different electrophysiological procedures. These drugs radically differ from conventional vitamin K antagonists, but also possess distinctive pharmacokinetics and pharmacodynamics that distinguish one NOAC from the other. Clinical evidence on the use of NOACs during CIED implant and transcatheter ablation procedures is still limited, but, at the same time, is rapidly expanding; there is a great need for extensive data derived from randomized-controlled trials and multicentre registries to better define the use of these drugs in interventional electrophysiology.

Keywords

Anticoagulation management**;** electrophysiological procedures**;** CIED implant; pulmonary vein isolation; radiofrequency ablation.

Introduction

The latest ESC guidelines on atrial fibrillation management [1] emphasize the growing importance of chronic anti-coagulation therapy in the setting of non-valvular atrial fibrillation (AF) to prevent thromboembolic stroke, defined on the basis of CHA_2DS_2VASc score. The clinical implications of these recommendations are that indication for anti-coagulation treatment has markedly expanded, especially among younger patients with AF. There is therefore a strong clinical mandate for the use of new oral anticoagulant drugs (NOACs) that are easier to manage than conventional vitamin K antagonists (VKAs). In this perspective, the therapeutic effectiveness of NOACs to prevent thromboembolic stroke combined with their good safety profile is of great interest. NOACs overcome some of the important limitations of VKA therapy, namely the long onset of action, prolonged half-life, as well as important interactions with other drugs and foods. These limitations become particularly relevant when VKA drugs must be managed in the peri-operatory setting. Specifically, interventional electrophysiology is concerned with cardiac implantable electric device (CIED) positioning and transcatheter ablation to treat cardiac arrhythmias. Careful oral anti-coagulation management is required to limit the time in which the patient remains at risk of thromboembolic events, but also to avoid peri-procedural bleeding. The European Heart Rhythm Association (EHRA) has recently issued a practical guide for the use of NOACs in different clinical settings [2]. This document has elaborated general recommendations for the management of NOACs for patients undergoing elective surgery and other interventions, including cardiac implantable electronic device (CIED) placement and transcatheter ablation procedures. These recommendations do not consider the particularities of CIED placement and some transcatheter ablation procedures such pulmonary vein isolation or ventricular tachycardia ablation procedures. Moreover, these new drugs are considered a clas**s** of new drugs with similar properties, that altogether differ substantially from conventional VKA; it is important to consider also that dabigatran, rivaroxaban, apixaban, and edoxaban present different pharmacological properties and, at the same time, available clinical data on their use in interventional electrophysiology remains scanty for all except maybe dabigatran. .

Therefore, the peri-procedural use of NOACs in the clinical setting of electrophysiological procedures, specifically CIED implantation and transcatheter ablation, is reviewed.

First, focus is placed on the pharmacological properties of NOACs are outlined to better comprehend and define their use in peri-procedural EP interventions. Second, by reviewing literature data, suggestions are provided on how to best manage NOACs during CIED positioning and in the peri-procedural setting of transcatheter ablation procedures.

Mechanism of action and pharmacokinetics of NOACs

CHA_2DS_2VASc score is a validated tool to quantify stroke risk in patients with atrial fibrillation. VKAs are the standard treatment for patients with atrial fibrillation and have demonstrated efficacy in the prevention of stroke. On the other hand, VKAs have a narrow therapeutic window and their metabolism vary among patients, with different responses and interactions with foods and drugs. Moreover, patients under VKAs therapy need routine laboratory monitoring. Differing from VKAs, NOACs present selective mechanisms of action and more stable and predictable pharmacokinetics. These properties provide the basis to simplify peri-procedural anti-coagulation management in patients with non-valvular atrial fibrillation.

Dabigatran is a potent, competitive, reversible direct inhibitor of thrombin, and is the active form found in plasma [3](Figure 1). After oral administration, dabigatran etexilate is rapidly absorbed and, by hydrolysis converted to dabigatran. It acts by inhibiting free and clot tied thrombin and is also able to reduce platelet aggregation stimulated by thrombin, thus accounting for their more effective action compared to indirect thrombin inhibitors, such as unfractionated heparin, which cannot inhibit thrombin linked to fibrin [4]. After oral administration dabigatran etexilate is absorbed from gastrointestinal tract and rapidly metabolized to dabigatran, but the absolute bioavailability of the molecule is low, averaging around 6,5%. Following oral administration, plasma concentrations grow rapidly, with peak concentration (Cmax) reached within 30 minutes after ingestion [5]. The administration of a meal does not appear to affect the bioavailability of dabigatran etexilate, but results in a delay of about two hours in the time required to reach the peak plasma concentration. Indipendently from concentration dabigatran etexilate is

bound to plasma binding proteins for about one third, with an half-life of approximately12-14 hours, which tends to be prolonged in patients with renal function impairment. Experimental studies, in fact, showed that dabigatran was largely eliminated by the kidneys (about 85%), while elimination through stools was estimated at 6% of the administered dose. Dabigatran is conjugated with formation of acylglucuronide, pharmacologically active and is eliminated primarily in the urine in unchanged form [6].

Rivaroxaban is the first oral anticoagulant acting as a direct inhibitor of factor Xa [7]. The inhibition of factor Xa caused by the molecule blocks at the same time the intrinsic and the extrinsic pathway of the coagulation cascade, blocking both the formation of thrombin and the development of clots. Rivaroxaban has no inhibitory effect on thrombin (activated factor II) and no actions on the aggregation of platelets [7,8]. After oral administration the drug is rapidly absorbed from the gastrointestinal tract. Absolute bioavailability is very high (80%), compared to that of dabigatran (3), with a peak concentration (Cmax) reached within 2-4 hours after tablet ingestion. Concomitant food intake does not affect drug's concentrations, but affects the peak plasma concentration by a delay of 2 hours [9].

The interindividual variability of the pharmacokinetics of rivaroxaban is between 30% and 40%. Rivaroxaban is transported bound to plasma binding protein, particularly albumin, for about 95% and is metabolized via CYP3A4, CYP2J2 and CYP-independent mechanisms. The half-life of the drug varies between 7 and 11 hours. About 50% of the drug is eliminated in the urine, with 30% of the administered dose excreted directly in the urine in unchanged form. The remaining 50% are excreted with stools [7].

Similar to rivaroxaban, apixaban is a potent, reversible, direct and highly selective inhibitor of factor Xa. The molecule does not require antithrombin III for antithrombotic activity. Apixaban inhibits both free factor Xa than that associated with the clot. It's also an inhibitor of prothombinase. The inhibition of factor Xa by the drug prevents the generation of thrombin and the development of thrombi. Apixaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. After oral administration apixaban is rapidly absorbed from the gastrointestinal tract, reaching maximum plasma concentration after 3-4 hours after ingestion. The

concomitant administration of food does not affect the molecule's concentration. The bioavailability of apixaban is around 50% for doses up to 10 mg and is carried by plasma binding protein approximately for 87%. Differently from dabigatran and rivaroxaban, apixaban is excreted mainly with stools, and renal excretion accounts only for 27% of elimination. The half-life of apixaban is about 12 hours and is metabolized by CYP3A4 and CYP3A5. The major biotransformation reactions are hydroxylation at the 3-ossopiperidinil and O-demethylation and the molecule is a substrate of the transport protein, P-glycoprotein (P-gp) [10].

Edoxaban is a potent, reversible direct inhibitor of factor Xa. It doesn't inhibit platelets aggregation but prevents platelets aggregation induced by thrombin. After oral administration edoxaban is rapidly absorbed by gastrointestinal tract. The effect of food on absorption is clinically irrelevant [11]. The bioavailability of the molecule is great and the short half-life is variable between 9 and 11 hours [8,12]. The drug is eliminated through kidneys (about 33%) and stool (about 66%) [12]. Several clinical studies showed that edoxaban at both dose of 15 mg or 30 mg /die reduced the incidence of venous thromboembolism after elective surgery for total hip replacement with a rate of bleeding similar to placebo [13,14]. Higher dosage increased tendency to bleed when administered to patients with atrial fibrillation [14]. The Phase III ENGAGE -AF- TIMI48 compared edoxaban to warfarin in the prevention of thromboembolism in patients with atrial fibrillation, showing non-inferiority of this NOAC compared with warfarin [15].

In summary, NOACs share some common pharmacological properties providing for simpler and easier peri-procedural anti-coagulation management. Rapid and predictable pharmacokinetics, limited interactions with foods and other drugs, as well as the fact that regular therapeutic effect is ensured without the need for monitoring, represent clear advantages of NOACs over conventional VKAs (Table 1)[15-18]. However, because NOACs anticoagulation effects are not monitored, correct management of these drugs depends on ascertained patient compliance to therapy. Furthermore, in a surgical setting, it is important to consider that no antidote is readily available [1] capable of rapidly antagonizing the effects of these drugs. Aspects pertaining to NOAC therapy initiation, therapy management in particular situations or according to particular patient characteristics has been detailed in the EHRA practical document [2].

Peri-procedural management of NOACs in patients undergoing CIED implant

Many patients on chronic anticoagulant therapy undergo implantation or substitution of a permanent pacemaker (PM) or an implantable cardioverter defibrillator (ICD), collectively known as cardiovascular implantable electrical devices (CIED). The perioperative management of anticoagulation therapy in these patients is a challenge that requires balance between the risk of acute thrombosis and perioperative bleeding, particularly pocket hematoma.

In this setting, the standard treatment has become to operate high-risk patients (CHA_2DS_2VASc score> 1) in uninterrupted warfarin with INR value within therapeutic range as opposed to heparin-bridging anticoagulation [25, 26]. The uninterrupted VKA approach has shown to consistently reduce pocket hematoma by 70% compared to bridging with heparin [19-21]. Continuing warfarin with a therapeutic international normalized ratio between 2-2.3 appears to be a safe and cost-effective approach for CIED surgery in most patients with moderate to high thromboembolic risk [19,20].

EHRA practical guide considers CIED positioning as a low bleeding risk intervention and propose to hold NOAC, in normal conditions, ≥ 24 hours before the intervention [2]. The document is particularly sensitive to dosage adjustment of dabigatran according to renal impairment. No consideration is however given to the fact that apixaban, which presents a shorter half-life, may be managed with shorter suspension intervals. The recommendations issued by the document are mostly empirical since clinical data on bleeding risk of patients chronically anticoagulated with NOAC in the peri-procedural setting of CIED implant or substitution are scarce and mostly limited to single center studies with small patient cohorts. A prospective observational study by Rowley [22] considered 25 patients, who underwent CIED implantation and received dabigatran for anticoagulation, showed that during the period of observation, no thromboembolic or bleeding complications developed, with no major bleeding complications within 30 days from surgery. One minor bleeding event (4%) occurred within 30 days of surgery in 1 patient who was also under dual antiplatelet therapy. Another recent study [23] compared uninterrupted dabigatran (in 48 patients) with uninterrupted warfarin (195 patients) during CIED procedure and showed a comparable incidence of pocket hematoma (around 2% in each group) between the two groups.

Based on the pharmacological properties of NOACs outlined previously, a reasonable approach (Table 2) may consist in interrupting the drug 24 hours (at least 1 half-life) before the CIED procedure. In the absence of bleeding complications, NOAC anticoagulation is then resumed 24 hours after the procedure. This simplified approach (Figure 2), similar to that already suggested by the EHRA document [2], limits the unprotected period to a maximum of 24-48 hours, while limiting potential increased bleeding complications in continuous anticoagulation conditions (uninterrupted warfarin or with LMWH bridging). Furthermore, this simple approach avoids the rapid bouts/surges of anti-coagulation characteristics of the heparin-bridging approach. At the actual state of knowledge, in contrast to what has been recently suggested [23], it may be prudent to avoid interventions under conditions of uninterrupted NOAC therapy. The absence of a readily-available, rapid-acting antidote should be a deterrent to consider this approach.

As already mentioned earlier, patients who undergo CIED implant are usually older patients with comorbidities, and therefore at increased bleeding and thromboembolic risk. The most sought for pharmacological properties should combine stable bioavailability, limited renal excretion as well as shorter half-life to limit the unprotected time frame of peri-operative thromboembolic risk, while, at the same time, containing bleeding risk. Taken together, apixaban presents more favourable pharmacokinetics compared to other NOACs (Table 1, Figure 2), because of its stable bioavailability, its limited renal excretion and shorter half-life. However, as already outlined above data on the use of apixaban in this setting is lacking and in the absence of clinical data these considerations remain speculative.

In summary, the pharmacological properties of NOACs make these drugs extremely appealing to use in the peri-procedural setting of CIED implant and substitution. Their use in this setting remains however ill-defined. Data derived from large clinical registries and randomized clinical trials (RCTs) are further needed to evaluate specifically safety of these drugs in this setting as well as defining which is the best and safest therapeutic regimen to follow for each NOAC. In the absence of such evidence, the use of NOACs in the peri-procedural setting of CIED procedures should be prudent, and confined to patients at moderately high thromboembolic risk.

Higher risk patients should be treated according to the well-established uninterrupted VKA approach as supported by a large body of clinical evidence [19,20].

Peri-procedural management of NOACs in transcatheter ablation procedures

The peri-procedural management of NOACs in transcatheter ablation procedures is still unclear. While anti-coagulation management in transcatheter ablation of arrhythmias in the right cardiac chambers is straightforward and follow what has been outlined for CIED positioning, because these ablation procedures are considered at low thromboembolic and bleeding risk [2]. Differently, more complex transcatheter ablation procedures such as pulmonary vein isolation and ventricular tachycardia ablation are considered high-risk procedures warranting careful anticoagulation therapy management [2].

The role of NOACs for trancatheter ablation has mainly been investigated in the clinical setting of PVI for the treatment of AF. When considering a patient with AF for PVI ensuring appropriate anti-coagulation is mandatory. Transcatheter ablation aiming PVI carries an additional thromboembolic risk. PVI implicates a long transcatheter ablation procedure in which multiple radiofrequency lesions are applied in the left atrium. This procedure therefore involves possible thrombus formation on the catheters and guide sheaths, endothelial denudation, local tissue inflammation, possible dislodgement of unrecognized left atrial thrombus, char formation on the catheter tip, and possible de novo clot formation due to atrial stunning if sinus rhythm is restored during the procedure either during ablation or by means of electrical cardioversion. These additional potential intraprocedural factors are controlled through continuous and rigorous anti-coagulation. It is now recommended to intervene under uninterrupted warfarin [1,24], with therapeutic INR, while administering intravenous heparin to maintain a level of ACT >300 seconds during the entire procedure. However, many centers continue to perform PVI under normal INR, with peri-procedural LMWH bridging. PVI also implicates double transeptal puncture and many RF lesions in the left-atrial cavity thus exposing the patient to risks of severe bleeding.

Knowledge on the use of NOACs in this setting remains rather limited, but is in rapid expansion (Tables 2 A and B). Most of the available evidence concerns dabigatran (Table 2 A)[25-32] and, more recently, some evidence has emerged on the use of rivaroxaban (Table 2 B) [31-33]. Tables 2 A and B summarize the main findings of the principal studies who have investigated the use of these drugs in the context of PVI compared to uninterrupted warfarin, with particular emphasis placed on peri-procedural anticoagulation regimen. Based on the current clinical evidence, and consistent with NOACs' pharmacological properties, the most common anti-coagulation regimen using NOACs is as follows: the NOAC is held 1 half-life duration before PVI procedure, i.e. 12 hours for dabigatran and 24 hours for rivaroxaban; during PVI ACT is maintained ≥ 300 seconds; the NOAC is resumed 4 hours after PVI procedure once hemostasis has been achieved. For completeness, it is worth mentioning that other contributions have considered differing peri-procedural anti–coagulation regimens: Winkle and colleagues [34] compared peri-procedural efficacy and safety of dabigatran in comparison, not to uninterrupted warfarin, but bridging regimen with unfractionated heparin (not cited in Table 2 A); other studies evaluated uninterrupted periprocedural anticoagulation regimen with NOACs [32,33]; in a recent RE-LY subanalysis the last dose of dabigatran was held a median of 49 hours before PVI procedure and not 12 hours before as is usually the case [35].

Overall, as detailed in Tables 2 A and B(25-, peri-procedural anticoagulation with NOACs in the setting of PVI has been demonstrated to be comparable to uninterrupted warfarin both in terms of efficacy as well as safety. This conclusion is in line with the findings of 2 recent meta-analysis studies [36-38]. In these contributions different peri-procedural anti-coagulation regimens in the setting of PVI were considered.

Even though clinical evidence supporting the use of NOACS in the setting of PVI is rapidly expanding, there are several considerations to be made. First, as high-lighted in the tables the large body of evidence issued derives mainly from retrospective observational data and not multicentre randomized studies. In this regard it is important to point out that the only multi-center study [27] enrolling 290 patients treated with dabigatran 150 mg bid showed an increased risk of

bleeding and a trend towards an increase incidence of thromboembolic complications compared to uninterrupted warfarin. A possible explanation for these results may lie in the multicentric design of the study that introduces varying patient-specific, technical and operator-dependent characteristics which yield differing results compared to single-center studies (in which these variables are more "controllable"). In this contribution [27], some patients with persistent AF and dilated left atrium were considered; some of these patients underwent extensive ablation in the left atrium which consisted not only in PVI, but also applying lines on the roof of the left atrium and along the mitral isthmus. Second, most published data concern the use of dabigatran, while the available data concerning rivaroxaban is limited. It is interesting to point out that a similar multicenter randomized study by the same group as the multicenter study with dabigatran [33], resulted in similar efficacy and safety by using uninterrupted rivaroxaban compared to uninterrupted warfarin. Third, although no data are thus far available for apixaban or edoxaban, based on the pharmacological properties of each NOAC (Table 1), some suggestions on how to manage NOACs in patients undergoing an elective high-risk transcatheter ablation procedure are provided (Table 3).

In summary, while the use of NOACs in this setting does look promising, as is the case for their use in CIED procedures, here too, there is a great need for further clinical evidence for their use derived from large multicenter registries and randomized clinical trials.

Conclusions

There is no doubt that NOACs simplify oral anti-coagulation management of patients CIED procedures and trancatheter ablation procedures because of their rapid onset of action and short therapeutic half-life. However, until their use is not founded on the basis of solid multicentre data in specific settings such as peri-procedural management of CIED procedures and transcatheter ablation, some degree of caution is warranted for their use. Furthermore, there is little guidance on which NOAC to prescribe considering specific patient characteristics. The present guidelines consider NOACs as a distinct class of drugs, because these drugs radically differ from conventional VKA. However, as presented in this review the different NOAC agents each have specific pharmacokinetics and pharmacodynamics that may render the use of one agent rather

than another in specific patient sub-sets. In older patients with comorbidities or in ablation procedures involving persistent or long-standing atrial fibrillation, therapy with VKAs is well established and should still be considered as first-line treatment.

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Table 1. New anticoagulant drugs approved for prevention of systemic embolism or stroke in patients with non-valvular atrial fibrillation. Modified from Heidbuchel et al (1).

	Dabigatran	**Apixaban**	**Rivaroxaban**	**Edoxaban**
Action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Bioavailability	6%	>50%	>80%	60%
Time to peak activity	2 hours	3 hours	2-4 hours	1-2 hours
Half-life	14-17 hours	5-9 hours (young), 11-13 (eldery patients)	8-15 hours	6-11 hours
Dose	150 mg bid 110 mg bid	5 mg bid 2,5 mg bid	20 mg qd 15 mg qd	15 mg 30 mg
Interactions	P-gp inhibitors and inducers	CYP3A4 inhibitors/inducers	CYP3Aç inducers, CYP3A4 and P-gp inhibitors	Potent inhibitor of Pgp
Renal elimination	80%	27%	33%	33%
Studies	RE-LY [16]	ARISTOTLE [18]	ROCKET-AF [17]	ENGAGE [15]

Table 2. Peri-procedural management of NOACs for elective CIED implantation*.

	Dabigatran		Apixaban		Edoxaban	Rivaroxaban	
	Stopped	Resumed	Stopped	Resumed	No data	Stopped	Resumed
CrCl ≥ 80 ml/min	≥ 24h	≥ 24h	≥ 24h	≥ 24h	No data	≥ 24h	≥ 24h
CrCl 50-80 ml/min	≥ 36h	≥ 24h	≥ 24h	≥ 24h	No data	≥ 24h	≥ 24h
CrCl 30-50 ml/min	≥ 48h	≥ 24h	≥ 24h	≥ 24h	No data	≥ 24h	≥ 24h
CrCl 15-30 ml/min	Not indicated		≥ 36h	≥ 24h	No data	≥ 36h	≥ 24h
CrCl < 15 ml/min	**Not indicated**						

CrCl: Creatinine clearance.
*Pacemaker or ICD implantation as well as electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia (including left-sided ablation via single transseptal puncture) are considered interventions with a low peri-procedural bleeding risk.
Modified from reference [2].

Table 3. Clinical evidence on the efficacy and safety of peri-procedural anticoagulation regimen using dabigatran (A) or rivaroxaban in the setting of transcatheter ablation for atrial fibrillation compared to uninterrupted warfarin. Number represent absolute values with percentages between parenthesis.

A) Dabigatran

Study design	NOAC regimen	n. of dabigatran treated patients	Thromboembolic events n (%)	Major bleeding events n (%)	Comments
Retrospective observational (Kaseno et al)(25)	-100 mg BID, held 12 h before; -ACT≥ 300 sec; -resumed 12-15 h after.	211	0 (0)	0 (0)	/
Retrospective observational (Snipeliski et al)(26)	-150 mg BID, held 12 h before; -ACT≥ 350 sec; -resumption?	31	0 (0)	0 (0)	Resumption unspecified
Multicenter prospective (Lakkireddy et al)(27)	-150 mg BID, held 12 h before; - ACT≥ 300 sec; - resumed 3 h after	145	3 (2.1)	9 (6.2)	Greater bleeding events compared to warfarin arm (p=0.019)
Retrospective observational (Kim et al)(28)	-150 mg BID, held 24 h before; - ACT≥ 300 sec; - resumed 4 h after.	191	0 (0)	4 (2.1)	No difference compared to warfarin
Retropective observational (Maddox et al)(29)	-150 mg BID, uninterrupted; -ACT≥ 350 sec;	212	1 (0)	0 (0)	No difference compared to warfarin
Retrospective Observational (Bassiourny et al)(30)	-150 mg BID, held 12-24 h before; -ACT≥350 sec; -resumed 3h after.	344	1 (0.3)	4 (1.2)	No difference compared to warfarin
Retropective observational (Eitel et al, 2013)(31)	-150 mg BID, held 12 h before; -ACT≥350 sec; -resumed 4h after.	144	0 (0)	0 (0)	No difference compared to warfarin
Retropective observational (Providencia, 2014)(32)	-150 mg BID, uninterrupted; - ACT ?	176	1 (0.6)	2 (1.1)	No difference compared to warfarin or rivaroxaban
TOTAL		**1454**	**6 (0.4)**	**19 (1.3)**	

B) Rivaroxaban

Study design	NOAC regimen	n. of rivaroxaban treated patients	Thromboembolic events n (%)	Major bleeding events n (%)	Comments
Retrospective observational (Eitel et al) (31)	- 20 mg OD, held 24 h before; -ACT≥ 300 sec; -resumed 12-15 h after.	16	0 (0)	0 (0)	No difference compared to dabigatran or warfarin
Multicenter prospective (Lakkireddy et al JACC 2013)(33)	-20 mg OD, uninterrupted; -ACT≥ 300 sec;	321	1 (0.3)	5 (1.6)	No difference compared to warfarin
Retropective observational (Providencia, 2014)(42)	-15 mg OD, UninterrupTed; - ACT≥ 300 sec;	188	2 (1.1)	3 (1.6)	No difference compared to warfarin or dabigatran
TOTAL		**525**	**3 (0.6)**	**8 (1.5)**	

Table 3. Peri-procedural management of NOACs for elective high risk transcatheter ablation procedures*.

	Dabigatran		Apixaban**		Edoxaban	Rivaroxaban	
	Stopped	Resumed	Stopped	Resumed	No data	Stopped	Resumed
CrCl ≥ 80 ml/min	12-24h	≥ 3h	12-24h	≥ 3h	No data	12-24h	≥ 3h
CrCl 50-80 ml/min	≥ 24h	≥ 3h	12-24h	≥ 3h	No data	12-24h	≥ 3h
CrCl 30-50 ml/min	≥ 36h	≥ 3h	12-24h	≥ 3h	No data	12-24h	≥ 3h
CrCl 15-30 ml/min	Not indicated		≥ 24h	≥ 3h	No data	≥ 24h	≥ 3h
CrCl < 15 ml/min	**Not indicated**						

CrCl: Creatinine clearance.
* Complex left-sided ablation (pulmonary vein isolation; ventricular tachycardia ablation) are considered interventions with a high peri-procedural bleeding risk. The time estimates of last intake and resumption of NOAC are derived specifically from the main literature data on NOAC management in the setting of PVI.
** no specific data available data for complex ablation procedures; the time estimates provided for apixaban in the table are empirical.
Modified from reference [2].

Figure legends

Figure 1. Mechanism(s) of action of new oral anticoagulants (NOACs) and vitamin K antagonists (VKAs) such as warfarin.

Figure 2. Comparison of the time course of drug plasma concentrations between three NOACs and warfarin.

Figure 1

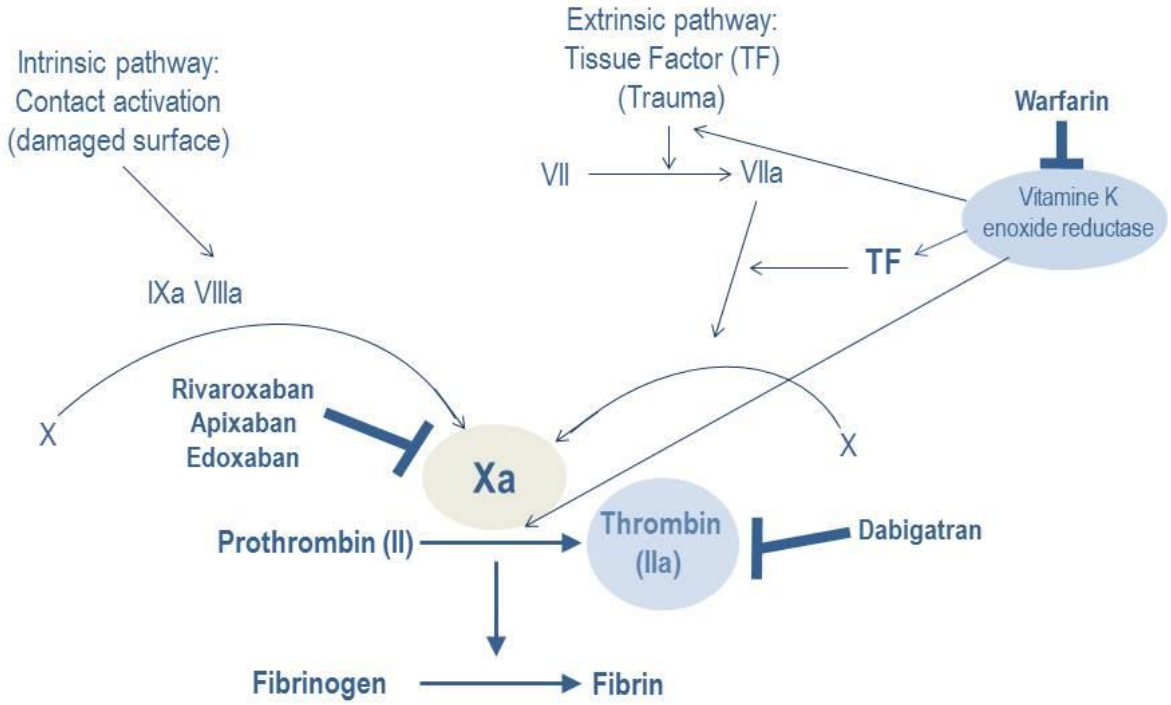
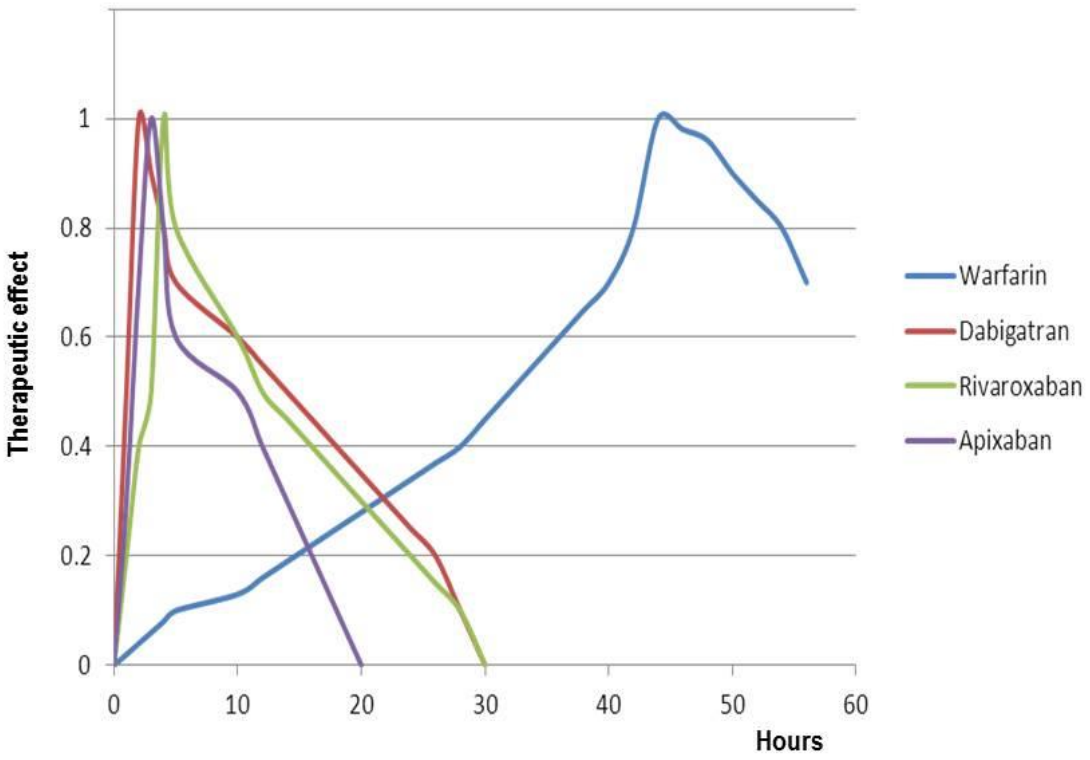

Intrinsic pathway:
Contact activation
(damaged surface)
Extrinsic pathway:
Tissue Factor (TF)
(Trauma)
Warfarin
VII
VIIa
Vitamine K
enoxide reductase
TF
IXa VIIIa
X
Rivaroxaban
Apixaban
Edoxaban
Xa
X
Prothrombin (II)
Thrombin
(IIa)
Dabigatran
Fibrinogen
Fibrin

Figure 2


Therapeutic effect
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60
Hours
Warfarin
Dabigatran
Rivaroxaban
Apixaban